et al. (*Immunological Reviews*, 62:119-158, 1982), **Andrews** *et al.* (*Blood*, 62:124-132, 1983) and **Rosenblum** *et al.* (U.S. Patent No. 5,631,348). In addition, claims 8-15 stand rejected under 35 U.S.C. §103(a) as being obvious over **Scheinberg** (U.S. patent 5,730,982) in view of **Thorpe**, **Andrews** and **Rosenblum.** These rejections are respectfully traversed.

Claims 8-15 pertain to a method of treating a neoplastic cell with a therapeutic dose of an immunoconjugate of an anti-CD33 monoclonal antibody and recombinant gelonin toxin. The treatment can be *in vivo*, *in vitro* or in bone marrow and can be used on animals including humans. The neoplastic cell can be taken from various disease conditions including acute and chronic myeloid leukemia and myelodysplastic syndromes, refractory anemias and lymphoid and undifferentiated leukemias. The claimed methods relate to retardation of neoplastic cell growth, prevention of recurrence of the neoplastic condition as well as extension of survival time of the host after treatment.

Tanimoto et al. and **Scheinberg** et al. teach an anti-CD33 monoclonal antibody M195, but **Tanimoto** did not characterize M195, stating that "the molecular nature of [this] target antigen remains unknown but it *appears* to be carried on the CD33 protein

p67 (abstract)." **Tanimoto** also briefly mentioned that M195 "may be useful in the clinical diagnosis of acute non-lymphoblastic leukaemia and in purging the bone marrow of acute non-lymphoblastic leukaemia" (abstract). Similarly, **Scheinberg** states that M195 may be a candidate of therapy of acute non-lymphoblastic leukaemia *in vivo* (abstract). However, **Tanimoto** and **Scheinberg** do not actually teach the use of M195 as a therapeutic agent by being a carrier for toxins and radioisotopes in treating acute non-lymphoblastic leukaemia. **Tanimoto** and **Scheinberg** do not teach the conjugation of M195 to recombinant gelonin or active fragments of gelonin.

U.S. Patent No. 5,730,982, issued to **Scheinberg**, teaches the use of M195-radioisotopes conjugates in cancer treatment. However, **Scheinberg** does not teach or suggest gelonin, or on the making and using of the M195-recombinant gelonin conjugate for cancer treatment.

Andrews et al. states that monoclonal antibodies may be useful for treating leukemia, but do not specifically teach the M195 anti-CD33 antibody, the conjugation of recombinant gelonin to M195 or the use of such conjugate against acute non-lymphoblastic leukaemia.

Rosenblum et al. teach gelonin and active fragments and the sequence of gelonin. **Rosenblum** does not teach M195 antibody or its conjugation to gelonin.

Thorpe et al. teach conjugation of antibodies to toxins like diphtheria toxin, abrin, ricin and gelonin, but **Thorpe** does not specifically teach the M195 monoclonal antibody, or the targeting of M195 to the CD33 antigen. According to **Thorpe**, "the cytotoxic properties of such conjugates [depend on] the different types of linkage used in constructing the conjugate....[which] influence its biological properties." (Page 120, lines 10-12). **Thorpe** gives the example of the method of direct linkage of a toxin directly to the antibody molecule, and states that "the cytotoxic potency of such conjugates is variable and .... unpredictable." (Page 120, lines 14 – 17).

Thorpe states that the toxic effects of abrin and ricin and the degree of protection from such toxic effects vary according to the cell type (Page 139, lines 9-10). In **Thorpe**, naturally-occurring gelonin was conjugated to anti-Thy antibodies, not to the anti-CD33 antibody, M195. Therefore, **Thorpe** offers no guidance as to the cytotoxic properties or lack thereof of the M195-recombinant gelonin conjugate of this application.

While the cited references **Tanimoto, Scheinberg, Thorpe, Andrews** and **Rosenblum** may teach the individual components of the instant invention, there is no teaching or suggestion to combine the components of M195 and recombinant gelonin to obtain the instant invention.

The effectiveness of an immunoconjugate depends on a number of factors including: (1) the type of toxin used; (2) the method of conjugation; (3) the monoclonal antibody; (4) the nature of the target cells; and (5) the mode of administration.

Loss of toxin potency or monoclonal antibody activity is not uncommon due to alteration in the binding site of the antibody. Even if the immunoconjugate retains functionality, it may not be an effective treatment if the target cells are unable to internalize it or high cytotoxicity may result if internalized by non-target cells.

Monoclonal antibodies to specifically target a cell have been known in the art for some time. Similary, various toxins including diptheria toxin, abrin, ricin and gelonin and their potential therapeutic values in cancer treatment have been known for years. Applicant does not dispute that it would be "obvious to try" producing the Applicant's immunotoxin nor does Applicant dispute that it would be "obvious to try" using Applicant's immunotoxin in

methods such as those recited by claims 8-15. Applicant does, however, most vigorously dispute that claims 8-15 are obvious under 35 U.S.C. §103(a) over any combination of the claimed references.

Although immunotoxins using various toxins and various targeting ligands have been known for some time, serous side effects have prevented clinical use of immunotoxins. These side effects include systemic toxicity in patients, incidences of vascular leak syndrome and human anti-human antibody responses. Considering the scientific history of immunotoxins due to these factors, a person having ordinary skill in this art would have expected the combination of a monoclonal antibody such as M195 with gelonin to produce the same problems as described.

Applicant hereby submit evidence in the form of a Declaration from the inventor, Dr. Michael Rosenblum pursuant to 37 CFR 1.132, demonstrating that the M195-gelonin immunoconjugate of this application has been administered (1) *ex vivo* to bone marrow cells from leukemic patients and (2) to patients with myeloid malignancies. Data contained in Dr. Rosenblum's Declaration show the efficacy and lack of significant toxicity of the M195-recombinant gelonin conjugate in a valid clinical setting.

Essentially, Dr. Rosenblum's studies clearly demonstrate that the M195-gelonin immunoconjugate is effective in suppressing leukemic bone marrow cell growth as well as being non-toxic *ex vivo* and *in vivo*. The results from Dr. Rosenblum's studies is in complete contrast to the expected manifestation of systemic toxicity well documented in the scientific literature. Applicant respectfully avers that the results from Dr. Rosenblum's studies illustrate an unexpected results and furthermore, that Dr. Rosenblum's Declaration strongly demonstrates the non-obviousness of the invention under 35 USC 103(a).

In view of the fact that the references cited by the Examiner do not collectively render the current invention obvious by teaching or suggesting the Applicant's claimed invention, Applicant respectfully submit that claims 8-15 are non-obvious. Accordingly, Applicant respectfully requests that the rejection of claims 8-15 under 35 U.S.C. §103(a) as obvious over the combination of **Scheinberg** (U.S. patent 5,730,982) **Thorpe**, **Andrews** and **Rosenblum** be withdrawn.

This is intended to be a complete response to the Office Action mailed November 15, 2001. If any issues remain outstanding,

the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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